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REVIEW ARTICLE

Urokinase Plasminogen Activator: A Prognostic Marker in Multiple Types of Cancer

MICHAEL J. DUFFY, MD, FRCPath,[1,2]* TERESA M. MAGUIRE, PhD,[1,2]
ENDA W. McDERMOTT, FRCSI, MCh,[1,2] AND NIALL O'HIGGINS, FRCSI, MCh[1,2]
[1]Department of Nuclear Medicine, St Vincent's Hospital, Dublin, Ireland
[2]Department of Surgery, University College of Dublin, Dublin, Ireland

Urokinase plasminogen activator (uPA) is a serine protease causally involved in cancer invasion and metastasis. Consistent with its role in cancer spread, uPA has been shown to be a prognostic marker in a variety of malignancies, especially breast cancer. Approximately 20 different groups have shown that high levels of uPA in breast tumor tissue predict poor outcome. As a prognostic marker in breast cancer, uPA provides information that is independent of traditionally used factors such as tumor size, tumor grade, axillary node status and estrogen receptor status. Furthermore, uPA is prognostic in node-negative patients, and a clinical trial is currently under way to assess whether uPA and its inhibitor, plasminogen activator inhibitor-1, can differentiate between the majority of node-negative breast cancer patients who are cured by surgery from the minority who might benefit from adjuvant therapy. uPA is also prognostic in other malignancies, such as gastric, colorectal, esophageal, renal, endometrial, and ovarian cancers. uPA may thus be a prognostic indicator for multiple types of adenocarcinoma.

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The prognosis of a cancer is primarily dependent on its ability to invade and metastasize. Cancer invasion and metastasis are multistep events involving local invasion of the extracellular matrix, angiogenesis, invasion of the blood vessel wall, survival of malignant cells in the vascular system, extravasation, and establishment of a secondary growth (Fig. 1) [1]. During most of these steps, natural barriers have to be degraded. It is now widely believed that the breakdown of these barriers is catalyzed by proteolytic enzymes released from the invading tumor [2,3]. One of the key enzymes involved in this degradation is urokinase plasminogen activator (uPA).

uPA is a serine protease with multiple activities [4,5]. Its best known action is catalysis of the conversion of the inactive plasminogen to plasmin. Plasmin, in contrast to uPA, is a broad-spectrum protease which degrades most substrates in the extracellular matrix [4,5]. Plasmin can also activate certain matrix metalloproteases [6], which in turn break down the collagen components in the matrix. In addition to these degradative functions, uPA exerts other activities that may enable it to play a role in invasion and metastasis. These include stimulation of cellular proliferation, enhancement of cellular migration, alteration of cellular adhesive properties and activation of specific growth factors [4,5]. Two of the growth fac-

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*Correspondence to: Michael J. Duffy, PhD, FRCPath, Department of Nuclear Medicine, St Vincent's Hospital, Elm Park, Dublin 4, Ireland. Fax No.: 353-1-2696018. E-mail: mjduffy@svherc.ucd.ie

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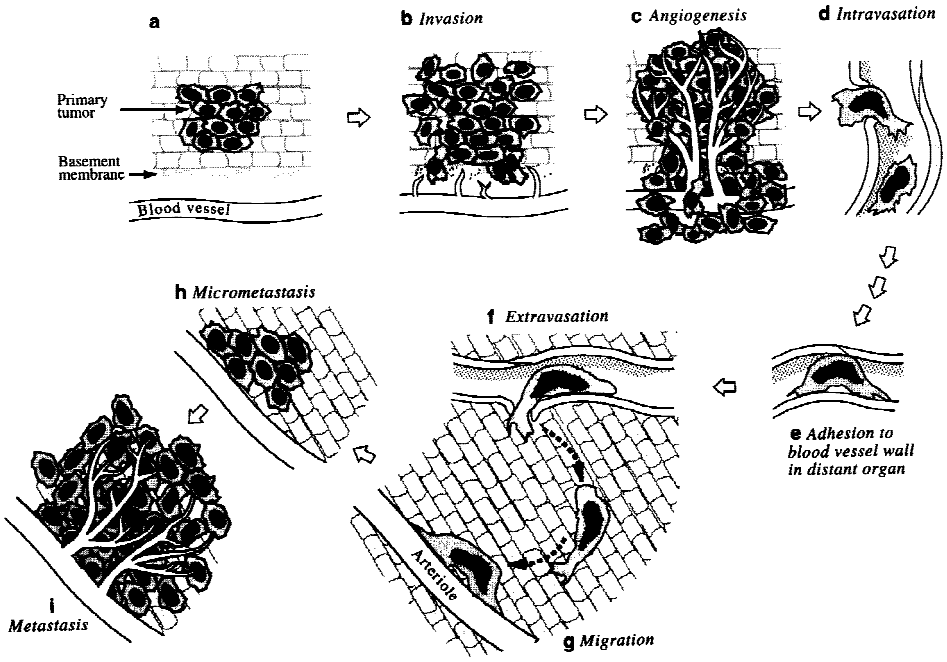

Fig. 1. Main steps in cancer invasion and metastasis. With permission, from the *Annual Review of Medicine,* Volume 49, 1998, by Annual Reviews.

tors activated by uPA, i.e., vascular endothelial growth factor (VEGF) and human growth factor (HGF), play a role in angiogenesis [7].

Most of these actions of uPA are mediated while the protease is attached to a membrane-bound receptor, known as uPAR [4]. Binding of uPA to its receptor accelerates activation of plasminogen to plasmin and concentrates the protease, allowing focal digestion of the surrounding matrix. Binding of uPA to receptor also leads to signal transduction with possible activation of gene transcription [4]. The modulating effects of uPA on cellular migration, proliferation, and adhesion may be mediated by this signal-transduction pathway rather than by a proteolytic mechanism [4].

In vivo, uPA activity is controlled by two inhibitors, plasminogen activator inhibitor-1 (PAI-1) and PAI-2 [4]. However, recent evidence suggests that both PAI-1 and PAI-2, like uPA, are multifunctional proteins. Thus, PAI-1, in addition to inhibiting uPA, binds to the extracellular protein vitronectin. Attachment to vitronectin appears to modulate cellular adhesion and migration. PAI-2, on the other hand, has not been shown to be involved in either adhesion or migration but is capable of inhibiting apoptosis [4].

Substantial evidence now implicates uPA in cancer invasion and metastasis [3–5]. Briefly, this evidence is as follows: (a) correlations exist between levels of uPA and metastatic potential in experimental systems, (b) inhibitors of uPA decrease the formation of metastasis, (c) antibodies against uPA inhibit metastasis, (d) administration of uPA to animals enhances metastasis, (e) transfection of non-metastatic cells with cDNA for uPA confers a metastatic phenotype on recipient cells, (f) inhibition of binding of uPA to its receptor inhibits or decreases metastasis, and (g) inhibition of uPA expression by antisense sequences prevents metastasis.

Over 10 years ago, we [8] originally proposed that proteases causally involved in invasion and metastasis might be markers of metastatic potential or prognosis in cancer. Evidence supporting this hypothesis has now been obtained for uPA in a variety of cancers. The aim of this review is to summarize the current status of this protease as a prognostic marker in different cancers.

BREAST CANCER

Approximately 20 different groups have now reported that high expression of uPA in primary breast cancer correlates with either a shortened disease-free interval or overall survival [9–29] (Table I). These results have been obtained with a number of different types of assay for uPA, including catalytic activity assays, enzyme-linked immunosorbent assays (ELISAs), immunohistochemistry, and in situ hybridization for uPA mRNA. Of the different assays, ELISA is most frequently used. Using ELISA, uPA levels correlate with patient outcome irrespective of the cut-off point used, i.e., whether an optimum, median, tertile, or quartile value is employed (Fig. 2) [30]. Absolute levels of uPA, i.e., when treated as a continuous variable, are also directly related to prognosis [15,30].

Different authors use different cut-off points for uPA,

TABLE I. Different Groups Showing Relationships Between High Levels of uPA and Either Disease-Free Interval or Overall Survival in Patients With Breast Cancer

Disease-free interval	Overall survival
Duffy et al., 1988 [9]	Duffy et al., 1990 [10]
Janicke et al., 1989 [11]	Schmitt et al., 1990 [12]
Spyratos et al., 1992 [13]	Cook et al., 1991 [14]
Foekens et al., 1992 [15]	Foekens et al., 1992 [15]
Bouchet et al., 1994 [16]	Grondahl-Hansen et al., 1993 [17]
Ferno et al., 1996 [18]	Umeda et al., 1997 [19]
Shiba et al., 1997 [20]	Knoop et al., 1998 [21]
Knoop et al., 1998 [21]	Peyrat et al., 1998 [22]
Peyrat et al., 1998 [22]	Grondahl-Hansen et al., 1997 [23]
Grondahl-Hansen et al., 1997 [23]	Broet et al., 1999 [24]
Broet et al., 1999 [24]	Bouchet et al., 1998 [26]
Kim et al., 1998 [25]	
Tetu et al., 1998 [27]	
Eppenberger et al., 1998 [28]	
Kute et al., 1998 [29]	

to separate patients with good and poor outcomes. These cut-off points vary from as low as 0.52 ng/mg protein to as high as 10 ng/mg protein [31]. Potential reasons for these differences include the following: (a) different uPA standards used in ELISAs, (b) different specificity of antibodies used in different assays, (c) different procedures for extracting uPA, and (d) different approaches for selecting the cut-off point.

As an indicator of patient outcome, most investigators find that the prognostic impact of uPA is independent of traditionally used markers such as axillary node status, tumor size, tumor grade, and estrogen receptor (ER) status [15,24,32,33]. In most studies with short-term follow-up, uPA is a more potent predictor of disease-free and overall survival than either tumor size or ER status and of similar strength to nodal status [32,33]. Furthermore, uPA also appears to be a better predictor of disease outcome than other proteases implicated in cancer spread, such as cathepsin B [34] or cathepsin D [33].

uPA is also of prognostic value in different subgroups of patients with breast cancer [35]. In particular, in multiple studies, it has been found to be a marker of aggressiveness in node-negative patients (Table II). In this subgroup of patients, as with total populations, the prognostic impact of uPA is generally found to be independent of tumor size, grade, patient age, ER status, and progesterone receptor (PR) status [22,24,36]. In addition to the node-negative subgroup, uPA levels have been shown to correlate with patient outcome in node-positive, premenopausal, postmenopausal, and ER-positive subgroups [35].

uPA is not only of prognostic value but may also be of predictive value in breast cancer. In 1995, Foekens et al. [37] first reported that high levels of uPA predicted resistance to tamoxifen in patients with advanced breast cancer. The association between high expression of uPA and lack of response to the antiestrogen appeared to be independent of ER and PR status [37,38]. However, the predictive ability of the protease was found only in a subset of patients, i.e., those with intermediate levels of steroid receptors (>10 fmol/mg protein for both receptors with at least one being not more than 75 fmol/mg protein) [37].

Because of the multiple and consistent reports linking high levels of uPA with adverse prognosis, because the findings that the protease is an independent prognostic

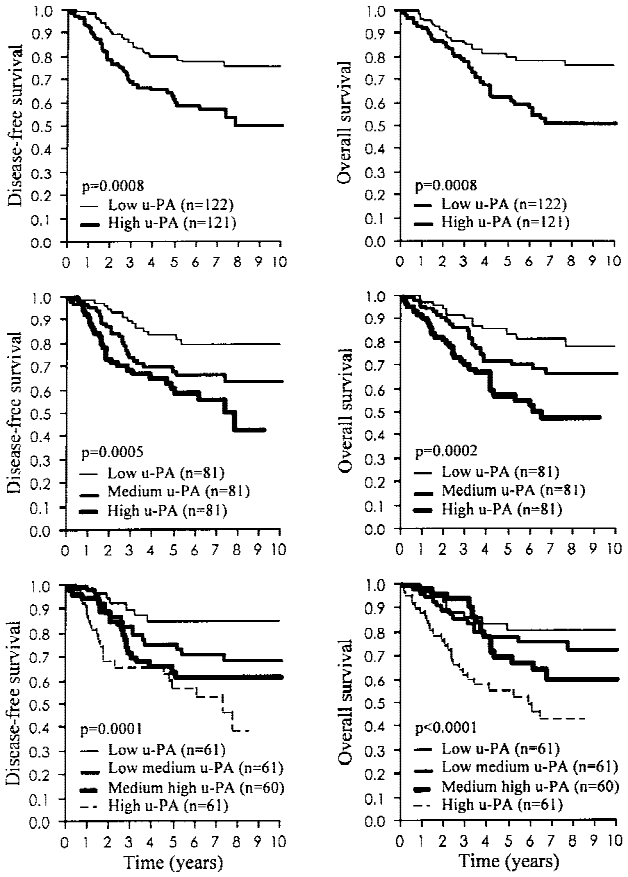

Fig. 2. Relationship between levels of uPA and outcome in patients with breast cancer using median, tertile, and quartile values as cut-off points. With permission from S. Karger (Basel), Duffy et al. [30].

TABLE II. Different Groups Showing Prognostic Value for uPA in Axillary Node-Negative Patients

Schmitt et al., 1990 [12]
Foekens et al., 1992 [15]
Peyrat et al., 1998 [22]
Broet et al., 1999 [24]
Kim et al., 1998 [25]
Bouchet et al., 1998, [26]
Eppenberger et al., 1998 [28]
Duffy et al., 1994 [35]

indicator, and particularly because its levels correlate with outcome in node-negative patients, this marker is now a potential candidate for routine use in the management of patients with breast cancer. However, before entering routine application, its clinical value should be evaluated in a multicenter prospective randomized study. Such a trial is presently under way in Germany, with over 600 patients enrolled [39]. In this trial, axillary node-negative patients with high concentrations of uPA (or its inhibitor PAI-1) are randomized either to receive six cycles of CMF (cyclophosphamide, methotrexate, and fluorouracil) or to be observed only. Patients with low levels of uPA/PAI-1 are not being treated. This trial aims at (a) confirming the prognostic value of uPA in node-negative patients and (b) identifying the minority of node-negative breast cancer patients that could benefit from adjuvant chemotherapy. The results of this study may eventually lead to a test that will prevent the administration of unnecessary and potentially toxic therapy to the majority of node-negative patients.

COLORECTAL CANCER

At least five different studies have reported a correlation between high levels of uPA and poor prognosis in patients with colorectal cancer [40–44]. In one of these studies, the cancer tissue:normal mucosa ratio for uPA was independent of tumor stage in predicting overall survival [43], while in another, uPA was found to be a marker of disease outcome in patients with Dukes' B disease [41]. Dukes' B is perhaps the subgroup of colorectal cancer patients where new prognostic markers are most urgently required. Whether uPA will be able to detect the subgroup of aggressive Dukes' B patients who might benefit from adjuvant chemotherapy remains to be shown.

GASTRIC CANCER

The prognostic value of uPA in gastric cancer was originally shown in a prospective study of 76 patients with complete resection of gastric cancer [45]. In this preliminary study, uPA was a significant predictor of overall survival using univariate analysis. In a multivariate analysis containing tumor stage, nodal status, World Health Organization classification of tumor grade, and PAI-1, uPA was not related to patient survival [45]. These preliminary findings have now been confirmed in two larger studies [46,47]. In one of these latter studies, Heiss et al. [46] investigated the prognostic value of uPA in different subgroups of patients with gastric cancer. These authors found that high uPA levels correlated with poor survival in the early stages (pT1/2) but not in more advanced tumors (pT3/4), in those with lymph node involvement but not in those without, and in those with diffuse and mixed-type cancer but not in those with intestinal-type cancer.

ESOPHAGEAL CANCER

In adenocarcinoma of the esophagus, uPA levels were found to be inversely related to overall survival using both univariate and multivariate analyses [48]. With multivariate analysis, uPA was of greater prognostic impact than either distant nodal metastasis, regional lymph node involvement, tumor depth, or lymphatic invasion in predicting outcome. In squamous cell carcinoma of the esophagus, uPA staining intensity ranked second to lymph vessel invasion but was more potent than tumor size, nodal status, tumor grade, or blood vessel invasion in determining overall survival [49].

OTHER CANCERS

In preliminary studies, uPA has been shown to be a prognostic indicator in a variety of other cancers, including urinary bladder [50], adenocarcinoma of lung [51], cervical cancer of uterus [52], ovarian [53], renal [54], hepatocellular [55], pancreatic [56], gliomas [57] and soft tissue sarcomas [58].

CONCLUSION

Consistent with its role in cancer metastasis, uPA has been shown to be a prognostic factor for a variety of cancers. Of the different cancers studied to date, the strongest and most consistent evidence of a prognostic role exists with breast cancer. In this malignancy, uPA is both an independent prognostic indicator in total populations and a prognostic indicator in node-negative patients. Furthermore, it may be of value in predicting the response to tamoxifen in patients with advanced breast cancer. Further work is required to assess whether uPA can predict the response to adjuvant tamoxifen or other hormonal therapies. The present prospective trial ongoing in Germany should provide information as to whether uPA can select the minority of node-negative breast cancer patients who could benefit from adjuvant chemotherapy.

Other molecules associated with uPA, such as its inhibitors PAI-1 and PAI-2 and its receptor uPAR, have also been shown to relate to outcome in different malignancies. Paradoxically, high levels of PAI-1, which might be expected to prevent invasion and metastasis, are positively correlated with aggressiveness in a variety of different cancers [4,5]. High levels of PAI-2, on the other hand, correlate with good outcome, at least in breast cancer [4,5]. Elevated concentrations of uPAR, like those of uPA, are also associated with poor prognosis [4,5]. In breast cancer, however, uPA is a stronger predictor of outcome than uPAR [59].

Finally, as uPA is causally involved in cancer spread, it is a potential target for antiinvasive and antimetastatic therapies. Inhibition of cancer progression might be possible by either downregulating uPA expression, inhibit-

ing its activity, or preventing binding to its receptor. Each of these approaches has been found either to prevent or decrease the formation of metastasis in model systems [2–5]. Clinical trials using similar approaches are planned for human cancers within the near future.

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